Intracranial haemorrhage in children with inherited bleeding disorders in the UK 2003-2015: a national cohort study.

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Abstract

Introduction: Intracranial haemorrhage in children with inherited bleeding disorders is a potentially life-threatening complication and presents a significant therapeutic challenge.

Aim: To define the characteristics, management and outcomes of intracranial haemorrhage presenting in UK children ≤16 years of age with inherited bleeding disorders from 2003-2015.

Method: Retrospective analysis of children treated at UK haemophilia centres.

Results: Of 66 children presenting with ICH, 82% had haemophilia A or B, 3% VWD and 15% a rare IBD. The IBD was a severe phenotype in 91%. The rates of ICH were 6.4 and 4.2 per 1000 patient years for haemophilia A and B respectively. Median age at presentation was 4 months (33% neonates; 91% children <2 years of age). In neonates, delivery was spontaneous vaginal (SV) in 11, instrumental in 6, caesarean in 4 and unknown in 1. In children with haemophilia the risk of ICH after instrumental delivery was 10.6 times greater than after SV delivery. Trauma was more common in children >2years (67%) than in children 1 month-2 years (18%; p=0.027). Prior to ICH only 4.5% of children were on prophylaxis. 6% of haemophiliacs had an inhibitor. The median duration of initial replacement therapy was 15 days. Mortality was 13.5%. Neurological sequelae occured in 39% of survivors, being more common following intracerebral bleeding. In haemophilia survivors, 52% subsequently developed a FVIII inhibitor.

Conclusion: ICH occurs most frequently in children with severe IBDs, during the first 2 years of life and in children not receiving prophylaxis. ICH often occurs without documented trauma.

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Introduction.

Intracranial haemorrhage (ICH) in children with inherited bleeding disorders (IBDs) is a serious complication associated with significant mortality and long term neurological morbidity. Most previous cohort studies have been carried out in haemophilia [1—7], however registries and small case series have also documented ICH in other IBDs, particularly the rare IBDs, severe Factor (F) VII, FX and FXIII deficiency [8,9].

ICH has been estimated to occur in 3-4% of neonates with haemophilia and has been associated with trauma at delivery, leading to debate on the optimal mode of delivery [2, 9, 11-13]. The incidence of ICH in older children with haemophilia has been estimated previously at 2.02-7.96 per 1000 patient years [2], but is less well defined in the modern era where, at least in the developed world, prophylaxis commenced early in childhood is widespread and may offer protection against all types of bleeding [4,14]. In addition, published reports have varied significantly in terms of age inclusion criteria which may affect risk factor identification in specific age groups.

Historically, mortality following ICH was extremely high and even in more recent studies occurs in 20-25%, with neurological sequelae commonly reported [4, 5, 15-17].

Improvements in diagnosis, management and the widespread use of prophylaxis, particularly in severe haemophilia, might be expected to have influenced both the occurrence and the outcomes of ICH in children with IBDs. The aim of this study was to define the incidence, clinical characteristics, management and outcomes of ICH in a national cohort of children with IBDs attending UK haemophilia centres from 2003 – 2015, where prophylaxis is the standard care for severe phenotype IBD.

Methods

In this retrospective national cohort study, ICH in children with IBDs presenting between January 2003 and December 2015, were reported to the UK Haemophilia Centre Doctors' Organisation (UKHCDO) National Haemophilia Database (NHD), which collates data from all haemophilia centres under an agreement with the UK Data Protection Registrar. Follow up data was obtained from reporting centres on diagnosis, presentation, risk factors, management and outcomes.

Statistical analysis

Diagnosis-specific incidence was calculated using data from children registered with the UKHCDO born between January 2003 and December 2015. Follow-up was measured from date of birth to the date of ICH, date of death, date of deregistration from the NHD, date of 16th birthday, or 31st December 2015. Cumulative incidence for haemophilia was illustrated using Kaplan-Meier plots. Descriptive statistics included medians, ranges and frequencies. Differences in proportions between groups were tested for statistical significance using Fisher's exact test. The association between mode of delivery and ICH was analysed by calculating odds ratios adjusted for family history using the Mantel–Haenszel method, with a group of 254 non-ICH cases serving as controls. Due to potential variation in obstetric practice controls were selected from 6 geographically distinct UK Haemophilia Centres.

Results

Incidence and underlying diagnosis.
75 ICH events were reported to the UKHCDO between 2003-2015. Following data clarification and removal of duplicates, 66 children aged ≤16years with IBDs were confirmed to have presented with radiologically confirmed ICH to one of 20 UK Haemophilia Centres. 3 had recurrent ICH (1 multiple), resulting in a total of 71 events. Patient characteristics and underlying diagnoses are summarised in Table 1.

Table 1.

Of the 66 children with any reported ICH, the underlying diagnosis was haemophilia in 54 (82%) and a rare IBD in 10 (15%). Only 2 children (3%) had VWD and there were no reported episodes of ICH in children with platelet disorders. In 60 children (91%), the underlying IBD was classified as severe.

UKHCDO registrations of children born between January 2003 and December 2015 were used to calculate the cumulative rate of ICH. This comprised 1321 children with haemophilia, of whom 1096 had haemophilia A (severe=549) and 225 haemophilia B (severe=106). The overall cumulative rate of ICH was 6.0 per 1000 years (95%CI 4.6-7.9) for any haemophilia. For those with haemophilia A the incidence was 6.4 per 1000 patient years (95%CI 4.8-8.6) and for haemophilia B, 4.2 per 1000 patient years (95%CI 1.9-9.5). The corresponding figures in severe haemophilia were 12.6 per 1000 patient years (95%CI 9.3-17.1) for haemophilia A and 7.7 per 1000 patient years (95%CI 3.2-18.4) for haemophilia B. The cumulative incidence of ICH in severe haemophilia A and B is shown in Figure 1. 3/54 children with haemophilia and ICH born prior to 2003 were excluded from this analysis. UKHCDO registrations for rare IBDs included 299 children. Reliable estimates of ICH frequency were not possible due to the small number of ICH cases.

Figure 1.

Age at ICH presentation.
Of the 66 children with ICH, the median age at presentation of first ICH was 4 months (range: birth–15yrs; IQR: 7 days-7 months). Of these, 17 children (26%) presented in the first week of life, 5 (8%) between the end of the first week and the end of the first month and 38 (58%) between the end of the first month and the end of the second year of life but only 6 (9%) after the first two years of life. The median age of presentation of first ICH for the 54 children with haemophilia was 5 months (range: birth-

15yrs IQR: 4 days – 9 months) and for the 10 children with a rare IBD was 40 days (range: 12 days–8 months; IQR: 20 days–2.5 months). The overall frequency of first ICH in the 54 children with haemophilia was 1.3% in neonates (< 1 month of age) (haemophilia A: 1.4%, haemophilia B: 0.9%), increasing to 3.6% at 2 years of age (haemophilia A: 3.7%, haemophilia B: 2.7%) and 3.9% at 10 years of age (haemophilia A: 4.1%, haemophilia B: 2.7%).

There was no significant difference in the distribution of underlying diagnosis in those presenting at ≤1 month of age or > 1month of age (p=0.75). (Table 2). Sub-dural and intracerebral ICH were the most frequent sites of bleeding, both occurring in 48% of children.

Table 2.

Risk factors for ICH
Considering the 54 children with haemophilia, an inhibitor prior to presentation with ICH was reported in 3 children (6%). 51 (94%) of children with haemophilia were not on prophylaxis prior to first ICH. Of the remaining three children with haemophilia who were receiving prophylaxis, all were receiving FVII for haemophilia A and only one was under 2 years of age. One child with haemophilia A and an inhibitor was receiving regular treatment with activated prothrombinase complex concentrate. None of the 10 children with a rare ICH were receiving prophylaxis before first ICH. Of the 66 children with ICH 1 (1.5%) had a family history of ICH.

Neonatal ICH & Mode of Delivery.
Of the 22 children who presented with ICH as neonates (18 with haemophilia, 2 with rare IBD), only three (14%) were preterm (≤36 weeks gestation). Of the 12 children with no prior family history of an IBD, six (50%) had an instrumental delivery (Table 3). In those with a positive family history of an IBD, there were no instrumental deliveries, however ICH occurred in 2 children despite planned caesarean delivery. ICH also followed elective caesarean in one child with no family history.

Table 3.

18 children with haemophilia presented with ICH as neonates. Compared with non-ICH neonates (N=254), using spontaneous vaginal delivery without instrumentation as the reference group and adjusting for family history of haemophilia, they were 10.6 times more likely to have been delivered with instrumentation, (95% CI 2.0-54.7, $p < 0.005$). Using the same reference group the risk associated with all caesarean deliveries was 0.6 (0.2 -1.8, p=0.3), 0.6 (0.2-2.1, p=0.4) for elective CS and 0.4 (0.1-2.9, p=0.4) for emergency CS.

Trauma in children presenting after 1 month of age.
Of the 44 children who presented with ICH after the neonatal period, trauma before presentation was reported for 11 (25%) children, 2/24 (8%) children aged 1-6 months of age; 7/32 (18%) children aged 1-24 months of age and 4/6 (67%) children older than 24 months (p=0.027)). In two children aged 1-6 months, trauma was secondary to non-accidental injury (NAI).

Management

Of the 66 children with ICH, 22 (33%) underwent surgical intervention. This comprised craniotomy and evacuation in 16 children and insertion of a VP shunt or drain in 6 children. Excluding those who died during the first few days of treatment, the median duration of initial replacement therapy was 15 days (range 5–42 days; IQR 14-28 days).

Outcomes

Mortality.
There were 9 deaths associated with ICH, giving an overall mortality of 13.5%. Of the 9 children who died, 8 children had haemophilia A and 1 had severe FVII deficiency. Seven deaths occurred within the first week after ICH, while the other 2 occurred later.

Neurological morbidity.
Of the 59 children who survived the initial event (median follow up 6.9 years, range 116 days-12.8 years), 23 (39%) were reported to have neurological sequelae. This comprised motor weakness (5), cognitive problems (9), combined motor and cognitive problems (6), seizures (6), partial deafness (1) and visual problems (1). Poor neurological outcome was more common following intracerebral bleeding 16/26 (62%) as compared to those with subdural bleeds 6/30 (20%) *p=0.002*.

Recurrent ICH.
3/59 (5%) children who survived the initial event experienced at least one further ICH. Two children had two episodes and one child had a further three episodes. All recurrent bleeds occurred in children with haemophilia and in 2 this was associated with an inhibitor.

Inhibitor development in children with Haemophilia A.
Of the 47 haemophilia A children with ICH, 40 survived and were available for follow up monitoring. Overall 21 (52%) developed inhibitors after initial FVIII replacement, including 7/14 (50%) treated under 1 month of age.

Discussion.

In this cohort study, we have evaluated the clinical characteristics, management and outcomes of 66 children with IBDs presenting with ICH to 20 UK haemophilia centres from 2003 to 2015. The findings provide a unique insight into ICH in the era of comprehensive care where prophylaxis for severe is considered standard of care.

It is noteworthy that 82% of children with ICH had an underlying diagnosis of haemophilia A or B, whereas 16% had a rare IBD and only 2% had VWD. The underlying diagnosis in our survey cannot be completely accounted for by the background UK population frequencies of different IBD, since in the UKHCDO database, haemophilia A and B accounts for only around 30% of registered patients and the proportion of children with severe haemophilia accounts for only 37% of children registered with this disorder (2015-16 UKHCDO annual report). Instead, our findings suggest that a diagnosis of haemophilia A or B and severe phenotype are distinct risk factors for ICH.

We observed a cumulative rate of ICH in children with haemophilia ≤16 years of age of 6.0 per 1000 years (95%CI 4.6 - 7.9). Due to small patient numbers rates were not calculated for other individual disorders. In haemophilia, comparison of ICH rates in different published studies is hampered by variation in study design, particularly in relation to age inclusion criteria. In Ljung's 2007 review the incidence of ICH in haemophilia ranged from 2.90-7.96 per 1000 patient years derived from studies with different age inclusion criteria published from 1992-2007 [2]. The effect of age is illustrated in a subsequent study where Zanon et al reported a cumulative rate of ICH of 2.5 per 1000 in adults and children, however in a subgroup of children aged 0-10 years born between 2003-2008, the rate was higher at 6.4 per 1000 and therefore similar to our study [5]. In a US IBD cohort observed between 1998 and 2008, the risk of ICH was 3.90 per 1000 patients, however, this cohort included adults and excluded children under 2 years of age, which in our study had the highest incidence of ICH [4].

Our observations of ICH in children with severe FV, FVII, FX and FXIII deficiency are consistent with previous reports [8, 18-20]. While we were unable to calculate reliable incidence estimates for ICH in these disorders, previous case series suggest that the absolute risk of ICH in rare IBD may be individually high, particularly for severe FXIII deficiency. Our finding that ICH was uncommon in children with VWD and absent in these with inherited platelet disorders is in keeping with the low number of reported cases, suggesting that ICH is indeed rare in patients with disorders of primary haemostasis [21, 22].

In our cohort, more than 90% of ICH cases had an IBD that was classified as severe. This is similar to data from Traivaree et al where 91% of children with ICH had a severe phenotype IBD [3]. Zanon et al reported that severe haemophilia was associated with an age adjusted hazard ratio of 10.21, with the majority of bleeds in mild haemophilia occurring not in children but in older adults [5]. The paucity of ICH in children with mild haemophilia in this UK cohort suggests that baseline factor activity in mild-moderate disease not only reduces the risk of joint bleeding but may also offer protection against ICH, emphasising the potential protective effect of routine prophylaxis [4,14].

The predominance of ICH in young children in our cohort is highlighted by the median age at presentation of 4 months, with 91% presenting under 2 years of age. The predominance of ICH in younger children has not been a consistent finding, and while most studies report neonates to be at high risk, the relationship between ICH and age is less clear beyond the neonatal period [1,5]. Again, the age distribution in our study may reflect the protective effect of prophylaxis which in the UK is commenced before the third birthday in >90% of children with severe haemophilia [23]. Earlier onset of prophylaxis might therefore have the potential to reduce the risk of ICH.

Neonatal ICH, particularly in haemophilia, has been the focus of several previous publications. In 2007 Ljung estimated that neonatal ICH affected 3.5-4.0% of babies born with haemophilia [2]. In a more recent European study, Richards et al reported cranial bleeding in 3.5% of cases but ICH in only 0.9% [24]. Kulkarni et al reported data from the US where ICH related to delivery in babies under 2yrs occurred in 2.6% of cases [25]. Taken together with our survey frequency of 1.3%, these figures may suggest a trend towards some improvement compared with more historical data, possibly due to improvements in the management of haemophilia carriers.

The potential link between neonatal ICH and trauma at delivery has resulted in an ongoing debate regarding the optimal mode of delivery for known carriers and variation exists between recommendations in national guidelines [11-13, 26-28]. In this study we documented a higher risk of ICH following instrumentation at delivery but were unable to show a significant difference in risk between CS delivery and SVD. The association with instrumentation is in keeping with other data, both from normal pregnancies and in those with IBDs [29,30]. What remains less clear is whether SVD without instrumentation is associated with a greater risk of ICH compared with caesarean delivery. Data from normal pregnancies suggests that instrumentation is associated with the highest risk of ICH, while elective CS offers the lowest risk [30]. Studies in IBDs, mainly in haemophilia, have resulted in conflicting data, suggesting that the margin of difference may be small and that even elective CS delivery carries some risk of bleeding. Despite this uncertainty it is apparent that in the UK there has been a gradual increase in CS deliveries in haemophilia carriers [31].

Beyond the neonatal period trauma has often been reported as a risk factor for ICH [4]. In this study there was a significantly higher incidence of reported trauma in children over 2 years of age. The absence of reported trauma was particularly striking in the youngest children, many of whom were pre-mobile. While the absence of prophylaxis is likely to be contributory, it is possible that other undefined factors relating to the developing brain may also contribute. It is also important to exclude non-accidental injury, which can co-exist with IBDs as was documented in 2 cases in this cohort.

Mortality following ICH in this study was 13.5%, with most deaths occurring early. In most contemporary studies mortality following ICH has been around 20%, however this often includes data from both adults and children where mortality rates may differ. More recently Witmer et al reported data from the US covering the period 2002-2011 where mortality in males with haemophilia aged <21 years with ICH was much lower at 2.5% [7]. In a similar study by the same authors mortality in children was lower than in adults, although this study did not include children under 2 years of age [4]. It is not clear why mortality in our series is higher, however mortality was highest in neonates who may be at particularly high risk and accounted for 33% of reported cases. Poor neuro-cognitive outcomes were reported in 39% and were more common following intracerebral bleeds, emphasising the need for structured neuro-cognitive follow up [17].

ICH management includes high dose factor replacement therapy which represents an intensive exposure. In haemophilia A this was been shown to be a risk factor for inhibitor development, particularly when associated with initial exposure to FVIII [32,33]. Consistent with this, haemophilia A survivors in this study had a higher than expected risk of inhibitor development.

The main strength of this study is that it represents a national cohort and consists of a relatively large number of cases across all IBDs. Given the specialised nature of care in the UK, it is very unlikely that cases would have been managed out with haemophilia centres and data collection is therefore likely to be a true reflection of cases presenting during this period. The only potential limitation might relate to early deaths occurring prior to referral for specialist management.

Conclusion.

In conclusion in this UK cohort study ICH occurred most frequently in children with severe IBDs, during the first 2 years of life and in children not receiving prophylaxis. ICH often occurred without documented trauma and was associated with significant morbidity and mortality.

Authorship Contributions.

E.C. initiated the study, analysed the data and wrote the manuscript. J.A., P.C., M.M., J.P., M.R., O.T., M.W. & A.M. contributed to the study design, data interpretation and manuscript review. BP provided statistical analysis.

Conflicts of Interest.

PWC has received honoraria from CSL Behring, Bayer, Novo-Nordisk and Shire and has received research support from CSL Behring. All other authors stated that they had no interests which might be perceived as posing a conflict of interest.

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